



King's Research Portal

DOI:

[10.1111/bdi.12519](https://doi.org/10.1111/bdi.12519)

Document Version

Peer reviewed version

[Link to publication record in King's Research Portal](#)

Citation for published version (APA):

Petri, E., Bacci, O., Barbuti, M., Pacchiarotti, I., Azorin, J-M., Angst, J., Bowden, C. L., Mosolov, S., Vieta, E., Young, A. H., Perugi, G., & BRIDGE-II-Mix Study Group (2017). Obesity in patients with major depression is related to bipolarity and mixed features: evidence from the BRIDGE-II-Mix study. *Bipolar Disorders*.
<https://doi.org/10.1111/bdi.12519>

Citing this paper

Please note that where the full-text provided on King's Research Portal is the Author Accepted Manuscript or Post-Print version this may differ from the final Published version. If citing, it is advised that you check and use the publisher's definitive version for pagination, volume/issue, and date of publication details. And where the final published version is provided on the Research Portal, if citing you are again advised to check the publisher's website for any subsequent corrections.

General rights

Copyright and moral rights for the publications made accessible in the Research Portal are retained by the authors and/or other copyright owners and it is a condition of accessing publications that users recognize and abide by the legal requirements associated with these rights.

- Users may download and print one copy of any publication from the Research Portal for the purpose of private study or research.
- You may not further distribute the material or use it for any profit-making activity or commercial gain
- You may freely distribute the URL identifying the publication in the Research Portal

Take down policy

If you believe that this document breaches copyright please contact librarypure@kcl.ac.uk providing details, and we will remove access to the work immediately and investigate your claim.

Obesity in patients with major depression is related to bipolarity and mixed features: evidence from the BRIDGE-II-MIX study.

Eleonora PETRI¹, Olivia BACCI¹, Margherita BARBUTI^{1,2}, Isabella PACCHIAROTTI², Jean-Michel AZORIN³, Jules ANGST⁴, Charles L. BOWDEN⁵, Sergey MOSOLOV⁶, Eduard VIETA², Allan H YOUNG⁷, Giulio PERUGI¹ for the BRIDGE-II-Mix Study Group.

¹University of Pisa, Pisa, Italy

²Barcelona Bipolar Disorders Program, Hospital Clinic, University of Barcelona, IDIBAPS, CIBERSAM, Barcelona, Catalonia, Spain

³Hôpital Sainte-Marguerite, Marseille, France

⁴Psychiatric Hospital, University of Zurich, Switzerland

⁵University of Texas Health Science Center, San Antonio, USA

⁶Moscow Research Institute of Psychiatry, Russia

⁷King's College, London, UK

Corresponding author

Prof. Giulio Perugi,
Department of Clinical and Experimental Medicine
University of Pisa.
Via Savi 10, 56126, Pisa, Italia.
Tel: +39 050 992543 Fax: +39 05021581
Email: giulio.perugi@gmail.com

Running head

Obesity in patients with major depression.

Word count: 2568

Abstract

Objectives: BRIDGE-II-MIX study aimed to estimate the frequency of mixed states in patients with MDE according to different definitions. This post-hoc analysis evaluates the association between obesity and the presence of mixed features and bipolarity. **Methods:** 2811 MDE subjects were enrolled in this multicentre cross-sectional study. In 2744 patients, the body mass index (BMI) has been evaluated. Psychiatric symptoms, socio-demographic and clinical variables were collected, comparing the characteristics of MDE patients with (MDE-OB) and without obesity (MDE-NOB). **Results:** obesity ($BMI \geq 30$) was registered in 493 patients (18%). In the MDE-OB group, 90 patients (20%) fulfilled DSM-IV-TR criteria for BD, 225 patients (50%) fulfilled the criteria for bipolarity specifier, 59 patients (13%) fulfilled DSM-5 criteria for MDE with mixed features and 226 patients (50%) fulfilled Research-Based Diagnostic Criteria for a mixed depressive episode. Older age, history of (hypo)manic switches during antidepressant treatment, the occurrence of three or more MDEs, atypical depressive features, antipsychotic treatment, female gender, depressive mixed state according to DSM-5 criteria, comorbid eating disorders and anxiety disorders were significantly associated with MDE-OB group. Among (hypo)manic symptoms during the current MDE, psychomotor agitation, distractibility, increased energy and risky behaviors were the variables most frequently associated with MDE-OB group. **Conclusions:** In our sample, the presence of obesity in patients with MDE seems to be associated with a lifetime diagnosis of BD. These findings suggest that obesity in patients with MDE could be considered a possible marker of bipolarity.

Key words: Obesity, Major Depressive Episode, Bipolar Disorder, Mixed Features.

1. Introduction

One of the main challenges in the diagnostic assessment of mood disorders is the early detection of bipolarity and mixed features in patients with a major depressive episode (MDE), in order to distinguish unipolar depression from bipolar disorder (BD), with relevant clinical and treatment implications [1, 2]. In fact, several epidemiological and clinical studies reported that almost 40% of BD patients initially receive the incorrect diagnosis of major depressive disorder (MDD) [3-5]. In primary care settings, a careful screening for mixed features allows to the identification of BD in 21% to 26% of unipolar depressed patients [6, 7]. In the Bridge study on 5635 adults with an ongoing MDE, a total of 903 patients fulfilled DSM-IV-TR criteria for BD, whereas 2647 met the bipolarity specifier criteria [8-10]. Growing evidence suggests an increased prevalence of mood disorders and in particular BD among individuals who are overweight or obese compared to those with weight in the normal range [11, 12]. A relationship between depression, especially with atypical features, and obesity has been widely demonstrated [13-15]. Moreover, atypical symptoms in depressed patients have been associated with both obesity and BD [16]. Notably, obese (OB) patients have been shown to have a higher risk of developing MDD and BD [17]. On the other hand, the course of bipolar depression is frequently affected by the development of overweight and obesity, that could be related to the effects of psychotropic medications or comorbid diagnosis with eating disorders such as binge eating disorder (BED) [12, 18].

A recent meta-analysis of 9 cross-sectional epidemiological studies confirmed that obesity is associated with increased prevalence of BD, however the mechanisms and temporal sequence underlying this relationship are poorly understood [19]. Regarding gender differences, women showed higher rates of atypical features, as well as a

higher body mass index (BMI) than males, especially abdominal obesity [16]. Furthermore, the rate of obesity in women with BD has found to be higher than in men with BD [20]. The co-occurrence of BD and obesity seems to negatively affect the course and the long-term prognosis of BD [21]. Greater number of lifetime depressive and manic episodes, more severe and difficult-to-treat index affective episode, higher affective recurrence, predominantly depressive, and shorter time to relapse were more frequently reported in OB than in non-obese (NOB) BD patients [22]. A recent study sample of 571 consecutive patients with MDE suggested that obesity could be considered as a predictor of bipolarity [23]. However, to our knowledge, the prevalence of mixed features, according to the definition of the DSM-5 and the research based diagnostic criteria (RBDC), and bipolarity, according to the criteria of the specifier for bipolarity and the DSM-IV-R for BD, in OB and NOB patients with MDE has not been systematically investigated.

The objective of Bipolar Disorders: Improving Diagnosis, Guidance and Education (BRIDGE)-II-MIX [24-26] naturalistic study was to provide a reliable estimate of the frequency of mixed states in a large international sample of patients diagnosed with MDE according to several sets of criteria.

The aim of the present post-hoc analysis is to compare the characteristics of patients diagnosed with MDE who present a BMI ≥ 30 (MDE-OB) and patients with BMI < 30 (MDE-NOB). We aim to characterize the MDE-OB patients in order to clarify the correlation between mixed features, bipolarity and obesity. We will also discuss the possible clinical and treatment implications of this association.

2. Patients and methods

The BRIDGE-II-Mix Study was a multicentre, international, non-interventional, cross-sectional study. The recruitment procedure and the inclusion criteria have been described in a previous study [24]. From an initial pool of 2811 patients with MDE, BMI has been evaluated in 2744 patients. 493 (18%) patients presented a BMI ≥ 30 .

2.1 Data collection

In a single consultation the participating psychiatrists completed a case report form for each patient, incorporating inclusion criteria, socio-demographic variables (age, gender, marital status), biometrics values (height, weight), in- or out- patient status, history of psychiatric symptoms (mood symptoms, suicide attempts) and previous psychiatric hospitalizations. Features of the MDE, including bipolar symptoms listed in the DSM-IV-TR diagnostic criteria for BD, known risk factors for BD (e.g. family history of BD, early onset depression), previous response to ADs, psychiatric comorbidity, current treatment and functional status determined by the investigator using the Global Assessment of Functioning (GAF) were assessed [27].

The evaluation packet was explicitly structured to use skills that fully trained psychiatrists would have and routinely apply in conducting an initial evaluation of an acutely ill patient. No rating scales requiring calibration with a standard were incorporated. Raters were instructed to follow their usual practice, as training might have altered these practices and been seen as a biasing factor.

The primary objective of the BRIDGE-II-MIX study was to establish the frequency of depressive mixed states by analyzing all the relevant symptoms of either pole. After the publication of DSM-5, this was post-hoc defined as 1) the proportion of patients fulfilling DSM-5 criteria for MDE with mixed features (DSM-5-MXS) [28], and 2)

research based diagnostic criteria for mixed state (RBDC-MXS). RBDC-MXS are defined by the presence of MDE plus 3 out of the following 14 hypomanic symptoms for at least a week: Irritable mood, Emotional/mood lability, Distractibility, Psychomotor agitation, Impulsivity, Aggression (verbal or physical), Racing thoughts, More talkative/pressure to keep talking, Hyperactivity, Increased energy, Risky behavior, Grandiosity, Elation, Hyper-sexuality. The proportion of patients fulfilling criteria for BD according to the DSM-IV-TR and bipolarity specifier proposed by Angst et al. [5, 8, 9] was also identified. The bipolarity specifier attributes a diagnosis of BD to patients who experienced an episode of elevated mood or irritable mood or increased activity with at least three of the symptoms listed under Criterion B of the DSM-IV-TR, associated with at least one of the three following consequences: (i) unequivocal and observable change in functioning uncharacteristic of the person's usual behavior, (ii) marked impairment in social or occupational functioning observable by others or (iii) requiring hospitalization or outpatient treatment. No minimum duration was required and no exclusion criteria were applied.

2.2 Statistical analysis

Chi-square test was used for comparison between groups for categorical variables and Student's t-test for continuous variables. The univariate analysis involved many tests of statistical significance, raising the problem of type I errors. For this reason, we corrected for multiple comparisons and utilized a Bonferroni-corrected threshold for statistical significance. A stepwise backward logistic regression model was then used to identify the predictive value of the 14 current (hypo)manic symptoms on the presence of BMI ≥ 30 . The stepwise modeling procedure started with the full model and consisted, for each step, in eliminating the least statistically significant variable

from the model and re-computing the revised model, until all remaining variables were at $p < .1$. Odds ratios with 95% confidence intervals were used for observed associations. We used the statistical routines of SPSS Statistics 22.0 for Mac OS (SPSS Inc., USA).

3. Results

3.1 Differences in clinical variables between MDE-OB and MDE-NOB

According to the DSM-IV-TR criteria, a diagnosis of BD was detected more frequently in the MDE-OB group (19.9%) compared to the MDE-NOB group (15.8%) ($p = 0.033$). Considering the BD subtypes, a statistically significant difference was found regarding the diagnosis of BD-I, with prevalence rates of 14.1% in the MDE-OB group and 9.3% in the MDE-NOB group ($p = 0.002$). Conversely, there were no significant differences in the prevalence rates of BD-II subtype between the two groups. Regarding the frequency of mixed depression, 59 (13%) patients in the MDE-OB group and 151 (6.6%) in MDE-NOB group fulfilled the DSM-5 criteria for mixed states ($p < 0.001$). In addition, when RBDC criteria for Mixed Episode were applied, MDE-OB patients reported more frequently mixed features than MDE-NOB subjects ($p < 0.001$). The two groups significantly differed for age, with MDE-OB patients resulting older than MDE-NOB subjects ($p < 0.001$). Female gender was significantly more prevalent in the MDE-OB group than in the MDE-NOB group ($p = 0.001$). MDE-OB patients were more frequently married than MDE-NOB subjects ($p < 0.001$). MDE-OB patients had significantly higher rates of first-degree family history for BD compared to subjects in the MDE-NOB group ($p < 0.001$). MDE-OB patients presented more frequently psychotic features ($p < 0.001$) and atypical features ($p < 0.001$) than MDE-NOB patients. Moreover, MDE-OB patients reported more frequently three or more lifetime depressive episodes ($p < 0.001$), history of suicide attempts ($p = 0.026$) and current episode that lasts more than one month ($p = 0.011$) compared to the MDE-NOB subjects (*Table 2*). Regarding the psychiatric comorbidity, there were no statistically significant differences between the two groups with respect to the rates of alcohol-substance use disorders, ADHD and borderline personality disorder. Eating

disorders and anxiety disorders were significantly more frequent in the MDE-OB group in comparison to the MDE-NOB group [respectively 11.8% vs 6.1% ($p < 0.001$) and 34.0% vs 27.6% ($p = 0.006$)]. With respect to previous pharmacological treatments, MDE-OB patients were treated with more than three drugs contemporarily more frequently than the MDE-NOB patients ($p < 0.001$). Furthermore, they were more frequently prescribed antipsychotics ($p < 0.001$) and mood stabilizers ($p < 0.001$) than the MDE-NOB subjects. There were no statistically significant differences regarding AD treatment and benzodiazepines prescriptions between the two groups. As concern the past response to treatment with ADs, MDE-OB patients have presented more (hypo)manic switches compared to MDE-NOB subjects ($p < 0.001$). After the multivariate logistic regression analysis, the variables most strongly associated with the presence of obesity were age [$p < 0.001$; OR 1.02 (1.01-1.02)], history of (hypo)manic switches during AD treatment [$p = 0.005$; OR 1.46 (1.12-1.90)], comorbid anxiety disorders [$p = 0.049$; OR 1.26 (1.00-1.60)], antipsychotics treatment [$p = 0.025$ OR 1.29 (1.03-1.62)], marriage [$p < 0.001$; OR 1.48 (1.19-1.84)], female gender [$p = 0.004$; OR 1.43 (1.12-1.82)]; atypical features [$p = 0.002$; OR 1.78 (1.24-2.54)], comorbid eating disorders [$p = 0.010$; OR 1.61 (1.12-2.32)], psychotic features [$p = 0.39$; OR 1.44 (1.02-2.05)], occurrence of three or more MDEs [$p = 0.003$; OR 1.44 (1.13-1.82)], , and depressive mixed state according to DSM-5 criteria [$p = 0.019$; OR 1.52 (1.07-2.15)] (*Table 3*).

3.2 Differences in the frequency of (hypo)manic symptoms between MDE-OB and MDE-NOB

The MDE-OB patients showed 11 out of the 14 RBDC (hypo)manic symptoms with a significantly higher prevalence compared to the MDE-NOB patients ($p < 0.001$) (*Table 4*). In multivariate logistic regression analysis, (hypo)manic symptoms most strongly

associated with obesity were psychomotor agitation, distractibility, increased energy and risky behavior (*Table 5*).

4. Discussion

In our multinational sample of 2744 patients with MDE, obesity resulted to be relatively common (18%), in line with the results of previous studies, supporting the strong association between depression and obesity [23, 29-31]. Interestingly, we observed a significant association between BD and obesity, similarly to previous findings [19, 32]. In our sample, the frequency of BD varied substantially according to different diagnostic criteria. When bipolar specifier was applied, about half of the MDE-OB subjects presented BD in comparison with approximately 40% of MDE-NOB patients. We found that obesity was significantly associated with the presence of atypical depressive features [14, 33]. Symptoms such as leaden paralysis, increased appetite, overeating, oversleeping and reduced physical activity might explain the weight gain in atypical depressive patients [34]. Atypical features have been associated with both BD and BED [35]. Thus, the specific association between BD and obesity might be partly explained by these overlapping atypical symptoms. Our results also showed a relationship between obesity and female gender in MDE patients, similarly to previous findings [36]. Interestingly, women present more frequently depression with atypical features [16] and this association could represent the link between obesity and female gender. The relationship between obesity and BD has been associated with a predominant depressive polarity of BD [22, 37, 38]. Similarly, in our sample obesity was associated with a history of more than three previous MDEs, supporting the relevant role of depression in developing overweight. MDE-OB patients were more frequently married than MDE-NOB, maybe due to older age of this group of patients. Moreover, the positive relationship that we found between MDE-OB patients and older age, reported also in previous studies [32, 39, 40], could be partially explained by the exposure to psychopharmacological treatment over a longer time

period [41-43]. Noteworthy, in our sample antipsychotic treatment was significantly more frequent in MDE-OB group. Antipsychotics are known to be associated with obesity [44], even if other studies reported that about 40% of drug-naïve BD patients were obese or overweight [37]. Since BD-I patients are more likely to be treated with antipsychotics/mood stabilizers compared to BD-II patients [45], in our sample the higher prevalence of BD-I diagnosis in MDE-OB patients in comparison to BD-II diagnosis could be related to the psychotropic medications. However, there are insufficient data to define how much psychotropic treatment is associated with overweight in BD patients [46]. With regard to lifetime comorbid diagnosis, in accordance with the existing literature [47-49], we found that comorbidity with eating disorders and anxiety disorders was more frequently reported in MDE-OB patients than in MDE-NOB subjects. A recent post-hoc analysis of the BRIDGE-II-mix showed that comorbidities with eating disorders and anxiety disorders were more frequently associated with a BD diagnosis (50). In this sense, a possible association between obesity, eating disorders and bipolar spectrum disorders could be hypothesized, in line with previous findings [49]. This comorbidity has been associated with increased severity of eating behaviors, poorer prognosis for obesity and treatment resistance in BD [22, 49, 51]. In our sample, first-degree family history for BD, antidepressant-induced (hypo)manic switches and psychotic features were more frequent in MDE-OB patients than in MDE-NOB patients. Moreover, regardless of the diagnostic criteria applied, the presence of mixed features was significantly more prevalent in the MDE-OB patients than in MDE-NOB subjects. After the multiple logistic regression, DSM-5 mixed features resulted as the most significantly variable correlated with obesity. Taken together, these results might support the hypothesis of relationship between obesity and the bipolar spectrum. It has been

suggested that the presence of lifetime (hypo)manic symptoms and mood instability may lead to impulsive-addictive behaviors, such as uncontrolled eating [23]. In our sample, most of the RBDC (hypo)manic symptoms were more prevalent in the MDE-OB group compared to the MDE-NOB subjects. This association could represent a possible link between bipolar spectrum disorders and obesity.

The main strengths of the BRIDGE-MIX II study include the large sample size, and the wide range of care settings, both hospital and community, from eight countries across three continents. Narrow exclusion criteria help making the findings more generalizable. The major limitation is that the participating centres were not randomly selected, which may led to a bias through the inclusion of psychiatrists with a particular interest in mixed states. Furthermore, among comorbid eating disorders, the BED subtype was not specified. Moreover, the lack of complete biometric data (waist circumference) might lead to an under-detection of abdominal obesity, especially in women.

5. Conclusion

From the results of our study, MDE-OB seems to show higher rates of bipolarity and mixed features than MDE-NOB individuals, indicating that obesity could be investigated as a possible biomarker of bipolar spectrum disorders. The identification of individuals with MDE and obesity as subset of patients at higher risk of presenting mixed and hypomanic symptoms should lead to a more comprehensive clinical evaluation in order to achieve a prompt detection of bipolar spectrum disorders, with important clinical and treatment implications, such as tailored behavioral psychological interventions [52]. Further longitudinal data on different populations are necessary to better define the burden and the role of the association between obesity

and mood disorders on correct diagnosis, treatment response and clinical outcome.

6. Funding source

The sponsor of this study (Sanofi-Aventis) was involved in the study design, conduct, monitoring, and preparation of the final data base, but not in the content of this report. All investigators recruited received fees from the sponsor in recognition of their participation in the study on a per patient basis. The corresponding author had full access to all the data and had final responsibility for data analyses, preparation of the report, and the decision to submit for publication.

7. References

- [1] Grande I, Berk M, Birmaher B, Vieta E. Bipolar disorder. *Lancet* 2016; 387:1561-72.
- [2] Sole E, Garriga M, Valenti M, Vieta E. Mixed features in bipolar disorder. *CNS spectr* 2016; 29:1-7.
- [3] Ghaemi SN, Sachs GS, Chiou AM, Pandurangi AK, Goodwin K. Is bipolar disorder still underdiagnosed? Are antidepressants overutilized? *J Affect Disord* 1999; 52:135-44.
- [4] Ghaemi SN, Boiman EE, Goodwin FK. Diagnosing bipolar disorder and the effect of antidepressants: a naturalistic study. *J Clin Psychiatry* 2000; 61:804-8; quiz 9.
- [5] Angst J, Sellaro R, Stassen HH, Gamma A. Diagnostic conversion from depression to bipolar disorders: results of a long-term prospective study of hospital admissions. *J Affect Disord* 2005; 84:149-57.
- [6] Hirschfeld RM, Cass AR, Holt DC, Carlson CA. Screening for bipolar disorder in patients treated for depression in a family medicine clinic. *J Am Board Fam Pract* 2005; 18:233-9.
- [7] Manning JS, Haykal RF, Connor PD, Akiskal HS. On the nature of depressive and anxious states in a family practice setting: the high prevalence of bipolar II and related disorders in a cohort followed longitudinally. *Compr Psychiatry* 1997; 38:102-8.
- [8] Angst J, Gamma A, Bowden CL, Azorin JM, Perugi G, Vieta E, Young AH. Evidence-based definitions of bipolar-I and bipolar-II disorders among 5,635 patients with major depressive episodes in the Bridge Study: validity and comorbidity. *Eur Arch Psychiatry Clin Neurosci* 2013; 263:663-73.
- [9] Angst J, Gamma A, Bowden CL, Azorin JM, Perugi G, Vieta E, Young AH. Diagnostic criteria for bipolarity based on an international sample of 5,635 patients with DSM-IV major depressive episodes. *Eur Arch Psychiatry Clin Neurosci* 2012; 262:3-11.
- [10] Angst J, Azorin JM, Bowden CL, Perugi G, Vieta E, Gamma A, Young AH. Prevalence and characteristics of undiagnosed bipolar disorders in patients with a major depressive episode: the BRIDGE study. *Arch Gen Psychiatry* 2011; 68:791-8.
- [11] Barry D, Pietrzak RH, Petry NM. Gender differences in associations between body mass index and DSM-IV mood and anxiety disorders: results from the National Epidemiologic Survey on Alcohol and Related Conditions. *Ann Epidemiol* 2008; 18:458-66.
- [12] McElroy SL, Crow S, Biernacka JM, Winham S, Geske J, Cuellar Barboza AB, Prieto ML, Chauhan M, Seymour LR, Mori N, Frye MA. Clinical phenotype of bipolar disorder with comorbid binge eating disorder. *J Affect Disord* 2013; 150:981-6.
- [13] Lasserre AM, Glaus J, Vandeleur CL, Marques-Vidal P, Vaucher J, Bastardot F, Waeber G, Vollenweider P, Preisig M. Depression with atypical features and increase in obesity, body mass index, waist circumference, and fat mass: a prospective, population-based study. *JAMA Psychiatry* 2014; 71:880-8.
- [14] Glaus J, Vandeleur C, Gholam-Rezaee M, Castela E, Perrin M, Rothen S, Bovet P, Marques-Vidal P, von Känel R, Merikangas K, Mooser V, Waterworth DM, Waeber G, Vollenweider P, Preisig M. Atypical depression and alcohol misuse are related to the cardiovascular risk in the general population. *Acta Psychiatr Scand* 2013; 128:282-93.
- [15] Luppino FS, de Wit LM, Bouvy PF, Stijnen T, Cuijpers P, Penninx BW, Zitman FG. Overweight, obesity, and depression: a systematic review and meta-analysis of longitudinal studies. *Arch Gen Psychiatry* 2010; 67:220-9.
- [16] Lojko D, Buzuk G, Owecki M, Ruchala M, Rybakowski JK. Atypical features in depression: Association with obesity and bipolar disorder. *J Affective Disord* 2015; 185:76-80.
- [17] Simon GE, Von Korff M, Saunders K, Miglioretti DL, Crane PK, van Belle G, Kessler RC. Association between obesity and psychiatric disorders in the US adult population. *Arch Gen Psychiatry* 2006; 63:824-30.
- [18] McElroy SL, Crow S, Blom TJ, Cuellar-Barboza AB, Prieto ML, Veldic M, Winham SJ, Bobo WV, Geske J, Seymour LR, Mori N, Bond DJ, Biernacka JM, Frye MA. Clinical features of bipolar spectrum with binge eating behaviour. *J Affective Disord* 2016; 201:95-8.
- [19] Zhao Z, Okusaga OO, Quevedo J, Soares JC, Teixeira AL. The potential association between obesity and bipolar disorder: A meta-analysis. *J Affective Disord* 2016; 202:120-3.
- [20] Baskaran A, Cha DS, Powell AM, Jalil D, McIntyre RS. Sex differences in rates of obesity in bipolar disorder: postulated mechanisms. *Bipolar Disord* 2014; 16:83-92.
- [21] Lackner N, Bengesser SA, Birner A, Painold A, Fellendorf FT, Platzer M, Reininghaus B, Weiss EM, Mangge H, McIntyre RS, Fuchs D, Kapfhammer HP, Wallner-Liebmann SJ, Reininghaus EZ. Abdominal obesity is associated with impaired cognitive function in euthymic bipolar individuals. *World J Biol Psychiatry* 2016; 17:535-46.
- [22] Fagiolini A, Kupfer DJ, Houck PR, Novick DM, Frank E. Obesity as a correlate of outcome in patients with bipolar I disorder. *Am J Psychiatry* 2003; 160:112-7.
- [23] Vannucchi G, Toni C, Maremmani I, Perugi G. Does obesity predict bipolarity in major depressive patients? *J Affective Disord* 2014; 155:118-22.
- [24] Popovic D, Vieta E, Azorin JM, Angst J, Bowden CL, Mosolov S, Young AH, Perugi G. Suicide attempts in major depressive episode: evidence from the BRIDGE-II-Mix study. *Bipolar Disord* 2015; 17:795-803.

- [25] Perugi G, Angst J, Azorin JM, Bowden CL, Mosolov S, Reis J, Vieta E, Young AH for the BRIDGE-II-Mix Study Group. Mixed features in patients with a major depressive episode: the BRIDGE-II-MIX study. *J Clin Psychiatry* 2015; 76:e351-8.
- [26] Perugi G, Angst J, Azorin JM, Bowden CL, Caciagli A, Mosolov S, Vieta E, Young AH, BRIDGE-II-Mix Study Group. Relationships between mixed features and borderline personality disorder in 2811 patients with major depressive episode. *Acta Psychiatr Scand* 2015; doi: 10.1111/acps.12457.
- [27] Endicott J, Spitzer RL, Fleiss JL, Cohen J. The global assessment scale. A procedure for measuring overall severity of psychiatric disturbance. *Arch Gen Psychiatry* 1976; 33:766-71.
- [28] American Psychiatric Association. 5th ed. Washington, DC2013.
- [29] Elmslie JL, Mann JI, Silverstone JT, Williams SM, Romans SE. Determinants of overweight and obesity in patients with bipolar disorder. *J Clin Psychiatry* 2001; 62:486-91; quiz 92-3.
- [30] Faith MS, Matz PE, Jorge MA. Obesity-depression associations in the population. *J Psychosom Res* 2002; 53:935-42.
- [31] Stunkard AJ, Allison KC. Two forms of disordered eating in obesity: binge eating and night eating. *Int J Obes Relat Metab Disord* 2003; 27:1-12.
- [32] Goldstein BI, Liu SM, Zivkovic N, Schaffer A, Chien LC, Blanco C. The burden of obesity among adults with bipolar disorder in the United States. *Bipolar Disord* 2011; 13:387-95.
- [33] Levitan RD, Davis C, Kaplan AS, Arenovich T, Phillips DI, Ravindran AV. Obesity comorbidity in unipolar major depressive disorder: refining the core phenotype. *J Clin Psychiatry* 2012; 73:1119-24.
- [34] Perugi G, Akiskal HS, Lattanzi L, Cecconi D, Mastrocinque C, Patronelli A, Vignoli S, Bemi E. The high prevalence of "soft" bipolar (II) features in atypical depression. *Compr Psychiatry* 1998;39:63-71.
- [35] Angst J, Gamma A, Sellaro R, Zhang H, Merikangas K. Toward validation of atypical depression in the community: results of the Zurich cohort study. *J Affective Disord* 2002; 72:125-38.
- [36] Sutin AR, Zonderman AB. Depressive symptoms are associated with weight gain among women. *Psychol Med* 2012; 42:2351-60.
- [37] Maina G, Salvi V, Vitalucci A, D'Ambrosio V, Bogetto F. Prevalence and correlates of overweight in drug-naïve patients with bipolar disorder. *J Affective Disord* 2008; 110:149-55.
- [38] Fagiolini A, Frank E, Houck PR, Mallinger AG, Swartz HA, Buysse DJ, Ombao H, Kupfer DJ. Prevalence of obesity and weight change during treatment in patients with bipolar I disorder. *J Clin Psychiatry* 2002; 63:528-33.
- [39] Bond DJ, Kunz M, Torres IJ, Lam RW, Yatham LN. The association of weight gain with mood symptoms and functional outcomes following a first manic episode: prospective 12-month data from the Systematic Treatment Optimization Program for Early Mania (STOP-EM). *Bipolar Disord* 2010; 12:616-26.
- [40] Gurpegui M, Martinez-Ortega JM, Gutierrez-Rojas L, Rivero J, Rojas C, Jurado D. Overweight and obesity in patients with bipolar disorder or schizophrenia compared with a non-psychiatric sample. *Prog Neuropsychopharmacol Biol Psychiatry* 2012; 37:169-75.
- [41] McElroy SL, Frye MA, Suppes T, Dhavale D, Keck PE, Jr., Leverich GS, Altshuler L, Denicoff KD, Nolen WA, Kupka R, Grunze H, Walden J, Post RM. Correlates of overweight and obesity in 644 patients with bipolar disorder. *J Clin Psychiatry* 2002; 63:207-13.
- [42] Carvalho AF, Sharma MS, Brunoni AR, Vieta E, Fava GA. The Safety, Tolerability and Risks Associated with the Use of Newer Generation Antidepressant Drugs: A Critical Review of the Literature. *Psychother Psychosom* 2016; 85:270-88.
- [43] Torrent C, Amann B, Sanchez-Moreno J, Colom F, Reinares M, Comes M, Rosa AR, Scott J, Vieta E. Weight gain in bipolar disorder: pharmacological treatment as a contributing factor. *Acta Psychiatr Scand* 2008; 118:4-18.
- [44] Henderson DC. Weight gain with atypical antipsychotics: evidence and insights. *J Clin Psychiatry* 2007; 68 Suppl 12:18-26.
- [45] Tseng MM, Chang CH, Liao SC, Chen HC. Comparison of associated features and drug treatment between co-occurring unipolar and bipolar disorders in depressed eating disorder patients. *BMC Psychiatry* 2017; 17(1):81.
- [46] Keck PE, McElroy SL. Bipolar disorder, obesity, and pharmacotherapy-associated weight gain. *J Clin Psychiatry* 2003; 64:1426-35.
- [47] Akiskal HS, Akiskal KK, Perugi G, Toni C, Ruffolo G, Tusini G. Bipolar II and anxious reactive "comorbidity": toward better phenotypic characterization suitable for genotyping. *J Affect Disord* 2006; 96:239-47.
- [48] Perugi G, Toni C, Traverso MC, Akiskal HS. The role of cyclothymia in atypical depression: toward a data-based reconceptualization of the borderline-bipolar II connection. *J Affect Disord* 2003; 73:87-98.
- [49] Segura-Garcia C, Caroleo M, Rania M, Barbuto E, Sinopoli F, Aloï M, Arturi F, De Fazio P. Binge Eating Disorder and Bipolar Spectrum disorders in obesity: Psychopathological and eating behaviors differences according to comorbidities. *J Affect Disord* 2016; 208:424-30.
- [50] Barbuto M, Pacchiarotti I, Vieta E, Azorin JM, Angst J, Bowden CL, Mosolov S, Young AH, Perugi G. Antidepressant-induced hypomania/mania in patients with major depression: Evidence from the BRIDGE-II-MIX study. *J Affect Disord* 2017; 219:187-92.

- [51] Greenberg BR, Harvey PD. Affective lability versus depression as determinants of binge eating. *Addict Behav* 1987; 12:357-61.
- [52] Vieta E, Sanchez-Moreno J. Behavioural activation training for depression. *Lancet* 2017; 389:367.

Table 1. Diagnostic distribution and frequency of mixed states and bipolarity according to different definition in 2744 patients with a Major Depressive Episode with (MDE-OB) and without (MDE-NOB) BMI ≥ 30.				
	MDE-NOB (n = 2291)	MDE-OB (n = 493)	OR (95% CI)	p
Diagnostic Distribution of Bipolar Disorder				
DSM-IV Bipolar	362 (15.8%)	90 (19.9%)	1.32 (1.02-1.71)	.033
- DSM-IV Bipolar I	213 (9.3%)	64 (14.1%)	1.61 (1.19-2.17)	.002
- DSM-IV Bipolar II	149 (6.5%)	26 (5.7%)	0.88 (0.57-1.35)	ns
Bipolar Specifier	920 (40.1%)	225 (49.7%)	1.47 (1.20-1.80)	<.001
- Bipolar I Specifier	526 (22.9%)	164 (36.2%)	1.90 (1.54-2.36)	<.001
- Bipolar II Specifier	394 (17.2%)	61 (13.5%)	0.75 (0.56-1.00)	ns
Depressive Mixed State				
DSM-5 criteria ^a	151(6.6%)	59 (13.0%)	2.12 (1.54-2.92)	<.001
RBDC Mixed Depression ^b	929 (40.5%)	226 (49.9%)	1.46 (1.19-1.79)	<.001

Legend. ^a MDE + three non-overlapping hypomanic criteria; ^b MDE + three or more hypomanic symptoms.

Abbreviations. BMI: body mass index; RBDC: research based diagnostic criteria.

Table 2. Clinical Features in 2744 patients with a Major Depressive Episode with (MDE-OB) and without (MDE-NOB) BMI ≥ 30.				
	MDE-NOB (n = 2291)	MDE-OB (n = 493)	OR (95% CI)	p
Age, mean (S.D.)	43.4 (13.9)	47.1 (12.4)	t=5.38	<0.001
Gender, Female	1547 (67.5%)	342 (75.5%)	1.48 (1.18-1.87)	.001
Marital status, Married	1186 (51.7%)	281 (62.0%)	1.52 (1.24-1.87)	<0.001
First-Degree Family History of BD	317 (14.0%)	93 (20.7%)	1.60 (1.25-2.07)	<.001
(Hypo)manic switches with ADs	340 (14.8%)	117 (25.8%)	1.99 (1.57-2.54)	<.001
Psychotic Features	564 (24.6%)	157 (34.7%)	1.63 (1.31-2.01)	<.001
Atypical Features	132 (5.8%)	57 (12.6%)	2.36 (1.70-3.27)	<.001
Suicide Attempts	490 (21.4%)	119 (26.3%)	1.31 (1.04-1.65)	.026
≥ 3 MDE	1242 (54.2%)	316 (69.8%)	1.95 (1.57-2.42)	<.001
Current Episode >1 month	779 (34.0%)	183 (40.4%)	1.31 (1.07-1.61)	.011
First MDE <30 Years	1119 (52.2%)	231 (51.0%)	0.95 (0.78-1.17)	ns
Psychiatric comorbidity				
Anxiety Disorders	632 (27.6%)	154 (34.0%)	1.35 (1.09-1.68)	.006
Eating Disorders	138 (6.1%)	53 (11.8%)	2.07 (1.48-2.89)	<.001
Alcohol-Substance Use Dis.	199 (8.7%)	32 (7.1%)	0.80 (0.54-1.18)	Ns
ADHD	49 (2.2%)	12 (2.7%)	1.25 (0.66-2.36)	Ns
Borderline Personality Disorder	143 (6.2%)	39 (8.6%)	1.42 (0.98-2.05)	Ns
Previous treatments				
Antidepressants	1874 (81.8%)	374 (82.6%)	1.06 (0.81-1.38)	ns
Antipsychotics	748 (32.6%)	199 (43.9%)	1.62 (1.32-1.99)	<.001
Mood-Stabilizers	606 (26.4%)	168 (37.1%)	1.64 (1.32-2.02)	<.001
More than 3 drugs	707 (30.8%)	190 (41.9%)	1.62 (1.32-1.99)	<.001
Benzodiazepines	1046 (45.6%)	212 (46.8%)	1.05 (0.85-1.28)	ns

Abbreviations. ADs: antidepressants; ADHD: attention deficit and hyperactivity disorders; BD: bipolar disorder; BMI: body mass index.

Table 3. Multiple logistic regression backward procedure of clinical features, bipolarity and mixed state diagnosis on the presence of BMI ≥ 30 in 2744 subjects with Major Depressive Episode (MDE).

Variables in equation	Wald	p-value	OR (95% CI)
Age	14.525	<.001	1.02 (1.01-1.02)
(Hypo)manic switches with Ads	7.848	.005	1.46 (1.12-1.90)
Anxiety Disorders	3.860	.049	1.26 (1.00-1.60)
Antipsychotics	5.045	.025	1.29 (1.03-1.62)
Marital status, Married	12.310	.000	1.48 (1.19-1.84)
Gender, Female	8.453	.004	1.43 (1.12-1.82)
Atypical Features	9.993	.002	1.78 (1.24-2.54)
Eating Disorders	6.580	.010	1.61 (1.12-2.32)
Psychotic Features	4.251	.039	1.44 (1.02-2.05)
≥ 3 MDE	8.99	.003	1.44 (1.13-1.82)
Depressive mixed state (DSM-5)	5.467	.019	1.52 (1.07-2.15)

Legend. Wald = 227.909, df = 1, p <.001. Variables not included in the equation: more than 3 drugs, current episode >1 month, first-degree family history of BD, suicide attempts, mood-stabilizers.

Abbreviations. ADs: antidepressants; BMI: body mass index.

Table 4: Distribution of 14 current (hypo)manic symptoms in 2744 patients with a Major Depressive Episode with (MDE-OB) and without (MDE-NOB) BMI ≥30.				
	MDE-NOB (n = 2291)	MDE-OB (n = 493)	OR (95% CI)	p
Irritable mood	720 (31.4%)	181 (40.0%)	1.45 (1.18-1.79)	<.001
Emotional/mood lability	674 (29.4%)	153 (33.8%)	1.22 (0.99-1.52)	ns
Distractibility	525 (22.9%)	151 (33.3%)	1.68 (1.35-2.09)	<.001
Psychomotor agitation	330 (14.4%)	111 (24.5%)	1.93 (1.51-2.46)	<.001
Impulsivity	306 (13.4%)	98 (21.6%)	1.72 (1.39-2.31)	<.001
Aggression (verbal or physical)	298 (13.0%)	91 (21.0%)	1.78 (1.37-2.29)	<.001
Racing thoughts	246 (10.7%)	81 (17.9%)	1.81 (1.38-2.38)	<.001
More talkative/pressure to keep talking	238 (10.4%)	79 (17.4%)	1.82 (1.38-2.40)	<.001
Risky behaviour	147 (6.4%)	56 (12.4%)	2.06 (1.49-2.85)	<.001
Hyperactivity	164 (7.2%)	60 (13.2%)	1.98 (1.45-2.71)	<.001
Increased energy	137 (6.0%)	52 (11.5%)	2.04 (1.46-2.86)	<.001
Grandiosity	82 (3.6%)	23 (5.1%)	1.44 (0.89-2.32)	ns
Euphoria	97 (4.2%)	32 (7.1%)	1.72 (1.14-2.59)	.013
Hyper-sexuality	57 (2.5%)	17 (3.8%)	1.53 (0.88-2.65)	ns

Abbreviations. BMI: body mass index.

Table 5. Multiple logistic regression backward procedure of 14 current (hypo)manic symptoms on the presence of BMI ≥ 30 in 2744 subjects with Major Depressive Episode (MDE).			
Variables in equation	Wald	p-value	OR (95% CI)
Psychomotor agitation	8.180	.004	1.50 (1.13-1.97)
Distractibility	5.693	.017	1.34 (1.05-1.71)
Increased energy	3.897	.048	1.44 (1.00-2.08)
Risky behaviour	2.845	.092	1.37 (0.95-1.97)

Legend. Wald = 801.99, df = 1, $p < .001$. Variables not included in the equation: irritable mood, mood lability, impulsivity, racing thoughts, hyper-sexuality, aggression, more talkative/pressure to keep talking, hyperactivity, grandiosity, euphoria.

Abbreviations. BMI: body mass index.